Cystic fibrosis

DR BASSAM FUAD ALSELWI

Introduction

- Cystic fibrosis is an **autosomal recessive** disorder that affects epithelial cells of the respiratory , gastrointestinal and reproductive tracts and leads to abnormal exocrine gland secretions.

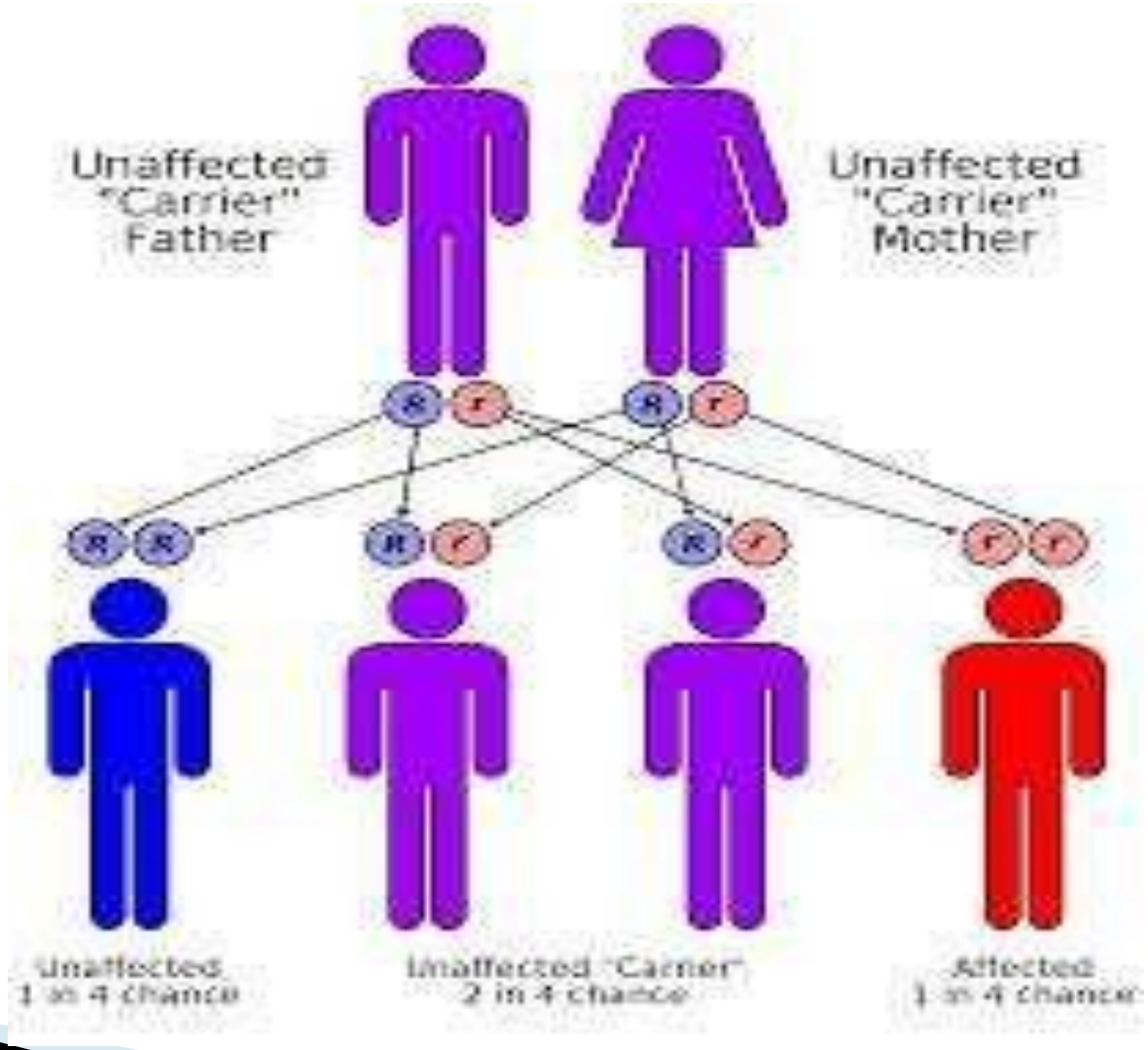
- An individual must inherit a defective copy of the CF gene (one from each parent) to have CF.

- Although it can affect many organ system, CF is particularly damaging to the lungs, leading to COPD in childhood and early adulthood.

Contd…

- Every person inherits two CF genes -- one from each parent. children who inherit a faulty gene from each parent will have cystic fibrosis.

- Children who inherit one faulty gene and one normal gene will be "CF carriers." Cystic fibrosis carriers usually have no symptoms of cystic fibrosis, but they can pass the faulty gene on to their children.


Unaffected
"Carrier"
Father
Unaffected
"Carrier"
Mother
R
r
R
r
R R
R r
R r
r r
Unaffected
1 in 4 chance
Unaffected "Carrier"
2 in 4 chance
Affected
1 in 4 chance

Contd…

- In cystic fibrosis (CF) there is an alteration in the **viscosity and tenacity of mucu**s produced at epithelial surfaces.

- The classical form of the syndrome includes increased broncho- pulmonary secretion and infection and pancreatic insufficiency, with a high sweat sodium and chloride concentration.

Epidemiology

- The frequency of CF is 1 in 2,000 to 3,000 live births, and there are approximately 30,000 children and adults with this disease in the United States(Cystic Fibrosis Foundation)

- Although CF was once considered a fatal childhood disease, approximately 38% of people living with the disease are 18 years of age or older .

Etiology /Pathophysiology

- CF is due to a mutation in the CF gene on chromosome 7.

- The CF gene encodes a protein known as the cystic fibrosis transmembrane regulator (CFTR)
- CFTR codes for a chloride channel which appear to inhibit the adjacent epithelial sodium channels

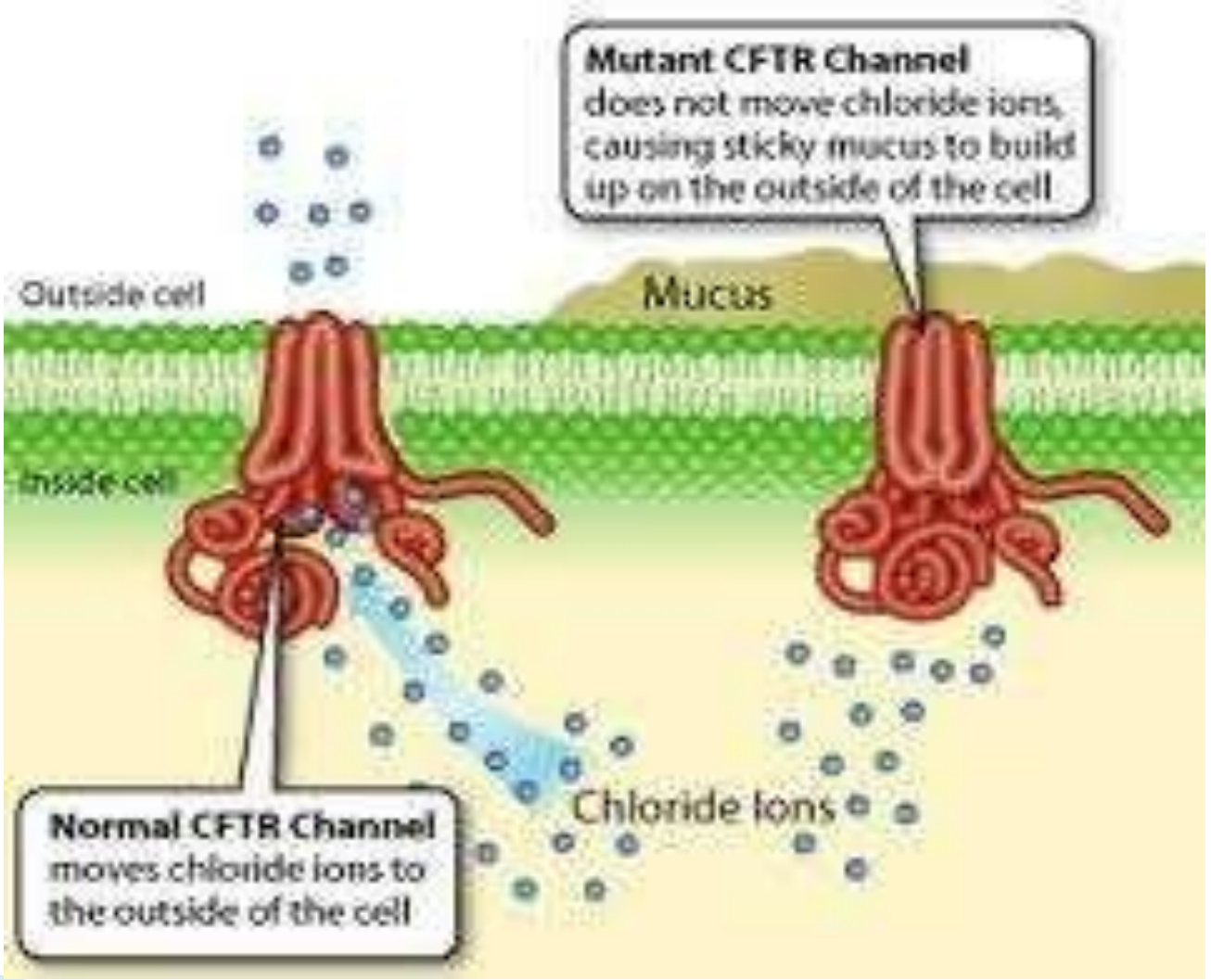
This influences salt and water movement across epithelial cell membranes.

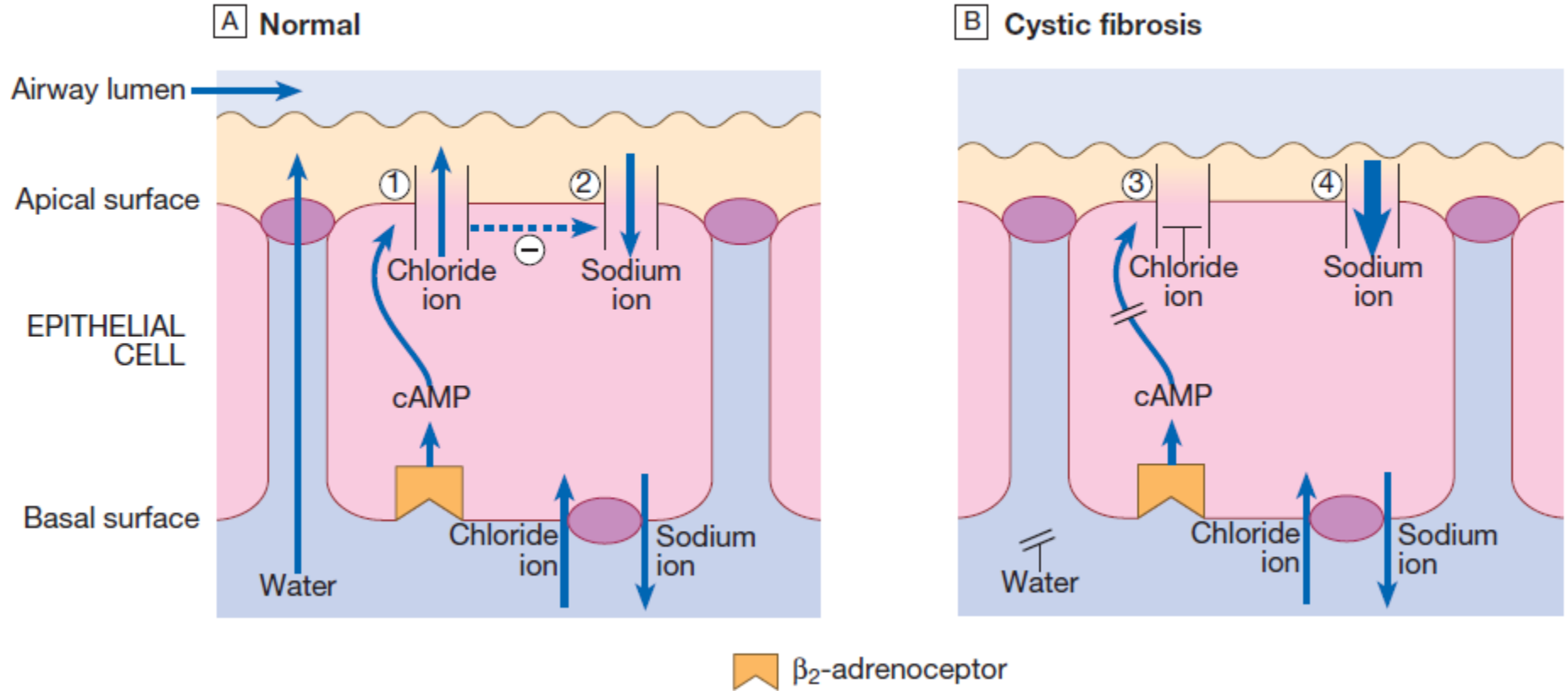
Etiology /Pathophysiology

- The abnormal CFTR protein in patients with CF leads to disruption of chloride channels on the cells
- This leads to reduced chloride secretion and loss of inhibition of sodium channels, with excessive sodium resorption

- The most common *CFTR* mutation in northern European and American populations is Δ*F508* but over 2000 mutations of this gene have now been identified.

Contd…


Mutant CFTR Channel
does not move chloride ions, causing sticky mucus to build up on the outside of the cell
Outside cell
Mucus
Inside cell
Chloride Ions
Normal CFTR Channel
moves chloride ions to the outside of the cell


A Normal
B Cystic fibrosis
Airway lumen
Apical surface
EPITHELIAL CELL
Basal surface
Chloride ion
Sodium ion
cAMP
Water
β2-adrenoceptor

Contd…

- Defective chloride transport cause more water and sodium reabsorption than normal. Relative Dehydration of the airway epithelium and abnormal airway-lining fluids thought to predispose to chronic bacterial infection and ciliary dysfunction, leading to bronchiectasis.
- Secretion in affected organs becomes thick and viscous obstructing the glands and ducts.
- Dilatation of the secretory glands damage to the exocrine tissue

Contd…

- The hallmark pathophysiologic effects of CF include.
- **Excessive mucous production in the respiratory tract with impaired ability to clear secretions and progressive COPD**:

✓ Atelectasis

✓ Infection

✓ Bronchiectasis

✓ Dilation of distal airway.

✓ Acute and chronic damage to the lung and scarring and fibrosis of lung tissue

➢ Chronic hypoxemia

Contd…

Pancreatic enzyme deficiency and impaired digestion

- Pancreatic insufficiency and impaired enzyme secretion ⇨ impaired digestion and absorption of protein, carbohydrate & fats

- Degenerative and fibrotic change ⟹ **DM**

Clinical Manifestations

Pulmonary manifestations

- usually lead to bronchiectasis in Childhood (Productive cough، wheezing,haemptysis)
- frequent exacerbations in upper lobes initially then throughout both lungs,
- Frequent chest infections .At childhood, the lungs are most commonly infected with Staphylococcus aureus; however, in adulthood, many patients become colonized with Pseudomonas aeruginosa.

Pulmonary manifestations

- Respiratory failure
- Spontaneous pneumothorax
- Haemoptysis
- Lobar collapse due to secretions
- Pulmonary hypertension
- Nasal polyps

Non pulmonary manifestations

Gastrointestinal and hepatic

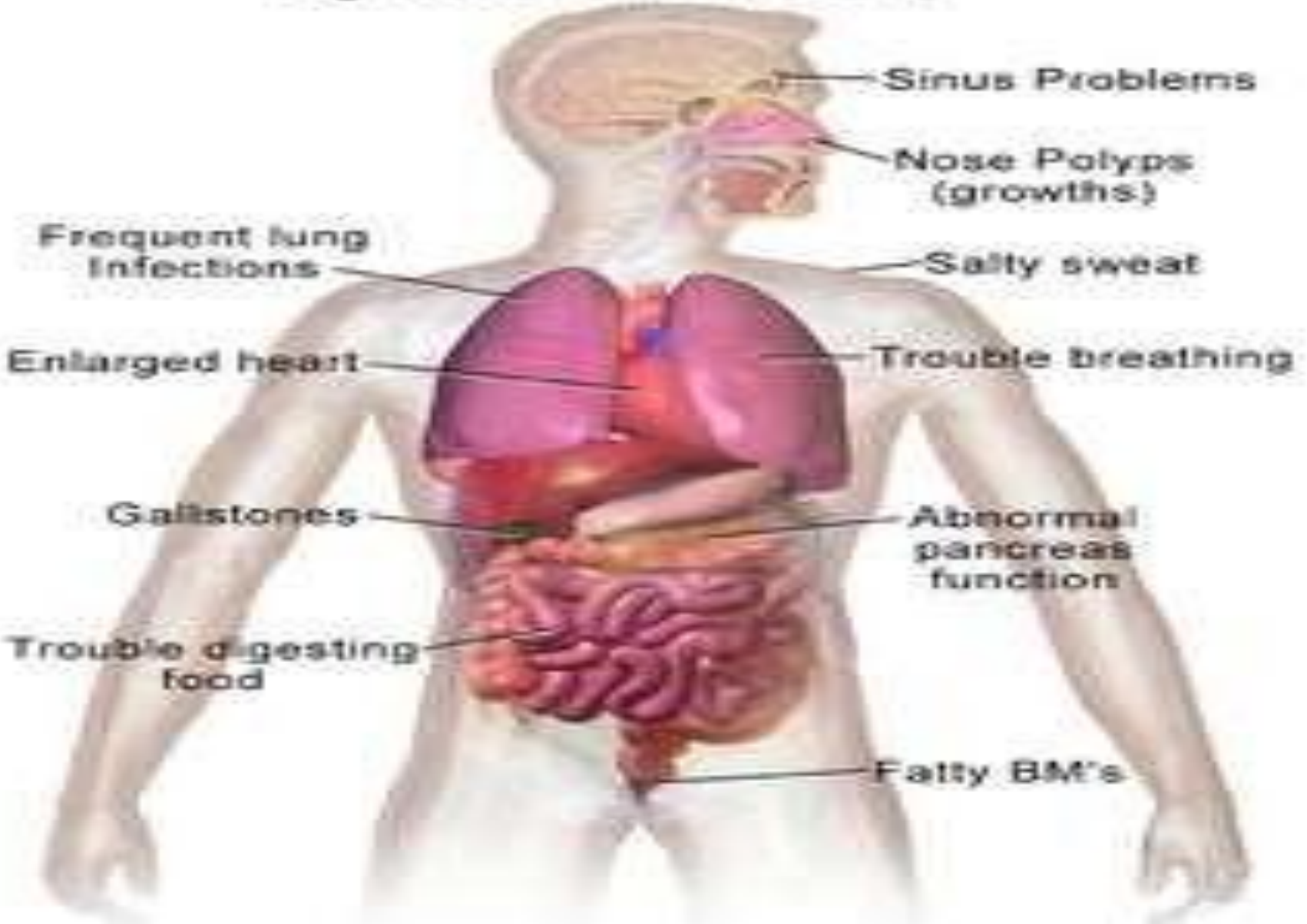
- Malabsorption and steatorrhoea
- Distal intestinal obstruction syndrome(Meconium ileus equivalent MIE)
- Biliary cirrhosis
- Portal hypertension, varices and splenomegaly
- Gallstones

Non pulmonary manifestations

Others

- Diabetes (25% of adults)
- Delayed puberty
- Male infertility
- Stress incontinence due to repeated forced cough
- Psychosocial problems
- Osteoporosis
- Arthropathy
- Cutaneous vasculitis

Health Problems with Cystic Fibrosis



Screening

- Neonatal screening for CF using
  - Immunoreactive trypsin
  - genetic testing of newborn blood samples
  - Pre-implantation and/or prenatal testing may be offered to those known to be at high risk.

Diagnosis and investigations

- the diagnosis was most commonly made from the clinical picture (bowel obstruction, failure to thrive, steatorrhoea and/or chest symptoms in a young child),

supported by sweat electrolyte testing and genotyping

Diagnosis and investigations

- sweat chloride

  Two samples of sweat chloride > 60 mmol/L

- *Genetic testing:*
  - Indications.
  - ✓ Intermediate results of sweat chloride test (40-60)
  - ✓ Family history of CF
  - ✓ Pre-pregnancy

- sputum culture

Diagnosis and investigations

- Radiological
  - CXR
  - CT SCAN of chest

- PFT
  - Obstructive pattern

- Others
  - ✓ CBC
  - ✓ LFTs

Management

- As that for bronchiectasis

General measures

- Stop smoking
- Adequate nutritional intake and supplementation if necessary
- Immunizations for influenza and pneumococcal pneumonia
- Confirm immunity to measles, pertussis, and rubella
- Long-term oxygen therapy in advanced cases
- Multi-disciplinary management addressing all aspects of disease in cystic fibrosis
- Patient and family counseling

Management

- ❖ Improve airway drainage
- ✓ Chest physiotherapy and chest clearance
- ✓ Mucolytic nebulization
- ✓ Nebulised recombinant human Dnase 2.5 mg daily
  Domase alfa (Pulmozyme)
- ✓ Nebulized hypertonic saline

Management

❖ Antibiotics

- ❑ Systemic Abs
- Treatment of exacerbations with considering Of pseudomonas and staph covering
- Regular oral azithromycin 500 mg 3 times a week
- ❑ Inhaled or neublized
- Patients colonised with P. aeruginosa
- ➢ Nebulised tobramycin or gentamycin 300 mg twice daily, given in alternate months

Management

- Bronchodilators
- Pancreatic enzyme supplements
- Multivitamins (including fat-soluble vitamins to treat associated conditions or complications (e.g. insulin, bisphosphonates)
- Lung transplant

Management

❖ Specific new treatment

- ❑ A CFTR ‘’ modulators
- The combination of oral ivacaftor a *CFTR* ‘potentiator’) ,lumacaftor and tezacaftor (a *CFTR* ‘corrector’) has been found to have modest short-term benefit in patients with DF508 mutations
- ❑ Somatic gene therapy for CF is also under development. Manufactured normal copies of the CF gene are ‘packaged’ in liposomes or virus vectors and administered to the airways by aerosol inhalation.

Thank you

Primary ciliary dyskinesia

Introduction

- A genetically and clinically heterogeneous disorder
- Autosomal recessive disease characterized by abnormal ciliary motion and impaired mucociliary clearance.
- Defects in the ultrastructure and function of cilia leads to ineffective ciliary mobility and abnormal mucociliary clearance
- Although the estimated prevalence is between 1 in 15 000 and 1 in 30 000, Studies suggest that PCD is still underdiagnosed.

Introduction

- When situs inversus, chronic sinusitis, and bronchiectasis occur together, an individual is said to have Kartagener's syndrome
- In 1933, Kartagner syndrome was first described
- Later, Afzelius noted that these patient have defects in the ultrastructure of cilia, and introduced the term immotile cilia.
- Later studies showed that disorganized motion, rather than immotile cilia, resulted in the ineffective ciliary beat, hence the term ciliary dyskinesia

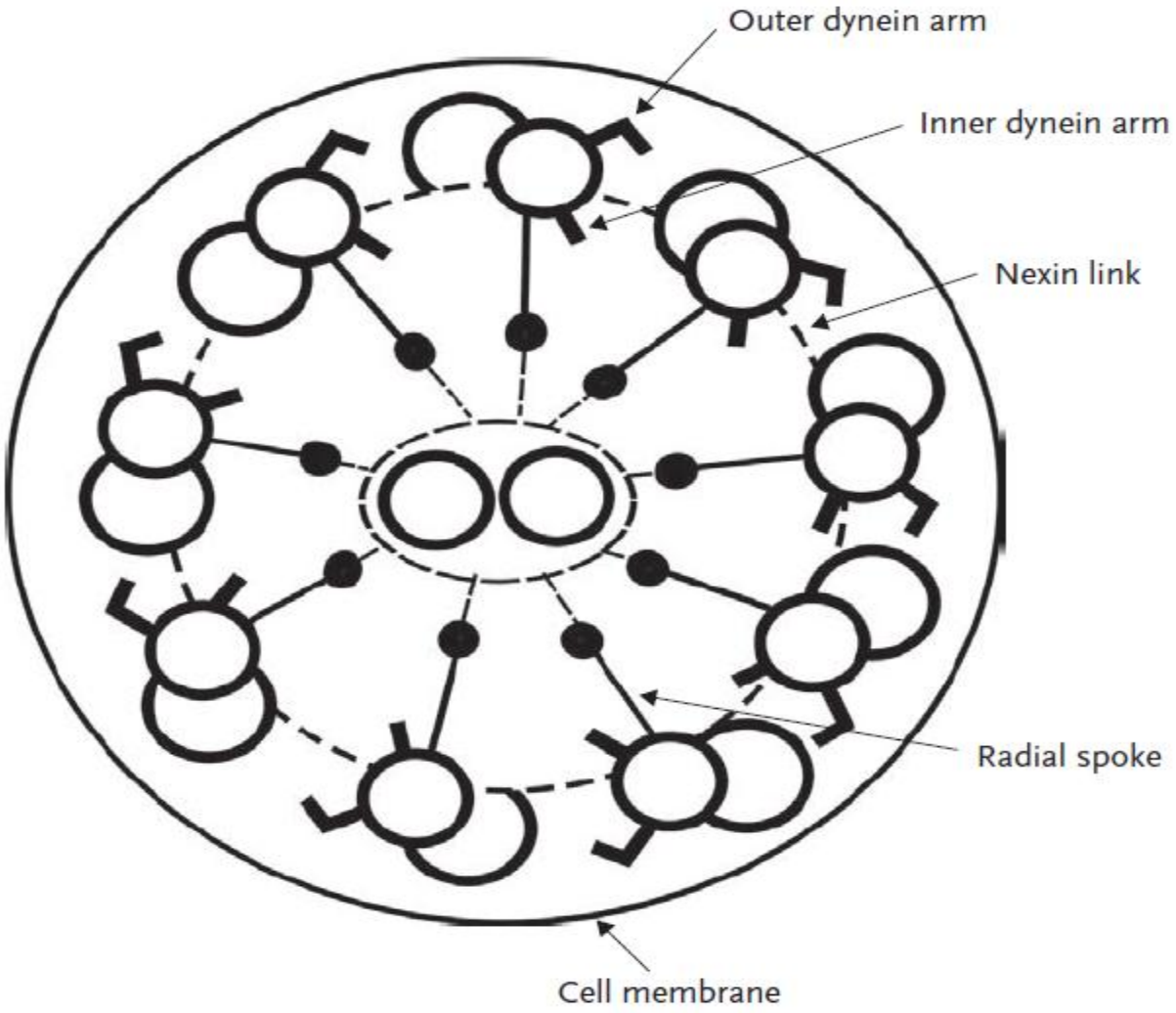


Figure 1
A cross section of the ciliary axoneme.

Ciliary structure and function

- In all the sinuses, mucus moves toward the natural ostia.
- Once mucus has drained from the sinuses into the nasal cavity, mucus flow is toward the nasopharynx.
- The cilia in the trachea and bronchi beat upwards, towards the throat
- The mucous blanket is cleared toward the nasopharynx every 10 to 15 minutes, and replaced by fresh mucus.

- Normal cilia beat frequency is 9 to 15 Hz
- results in a normal mucus velocity between 3 and 25 mm/min

Pathogenesis

- autosomal recessive disease.
- Defects in the ciliary component causing abnormal ciliary movement.
- The two most common genes mutated in PCD include DNAI1 (outer dyein arm intermediate chain) and DNAH5 (outer dyein arm heavy chain), both of which have been implicated in 30% to 38% of PCD patients
- Other mutations include:
  - Inner dynein arms (DNALI1)
  - Radial spoke head gene mutations (eg, RSPH4A, RSPH9)
  - Lack of Central core structures

Clinical presentation

- It commonly presents with neonatal respiratory distress, recurrent childhood pulmonary infections, chronic otitis media, and CRS.
- Most patients with PCD present in childhood (median age of diagnosis 5 to 5.5 years), but some present in adulthood (median age of diagnosis 22 years)

Clinical presentation

- Rhinosinusitis is a cardinal feature of PCD, occurring in almost affected individuals.
- Nasal polyposis is frequently present.
- Chronic sinusitis typically involves the maxillary and ethmoidal sinuses, as the frontal and sphenoid often fail to develop

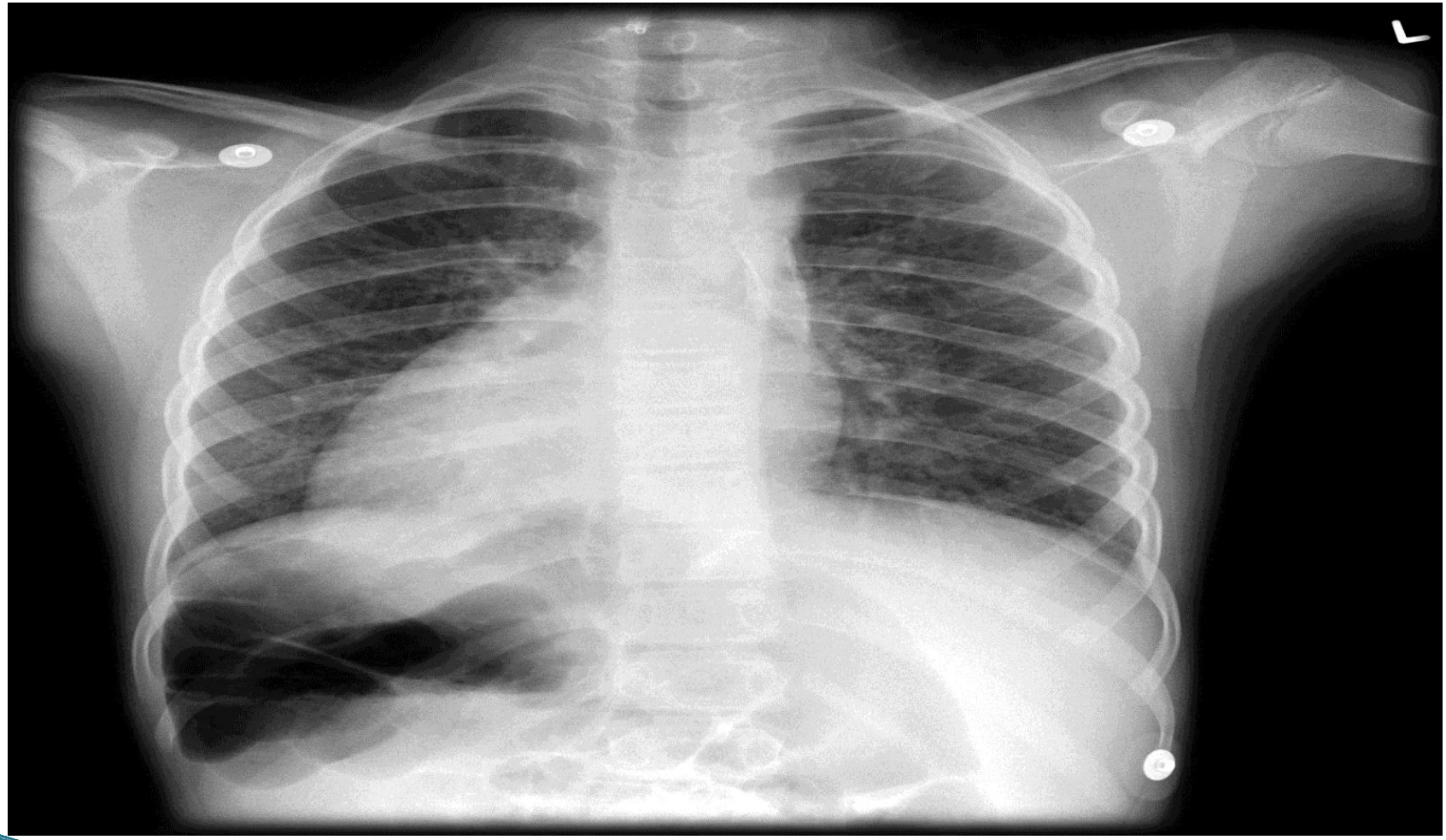
Clinical presentation

- Newborns with PCD often suffer from mild respiratory distress, (tachypnea or mild hypoxemia), and may require supplemental oxygen for a few hours to days after birth.
- Patients with bronchiectasis generally manifest chronic wet cough , auscultatory crackles and may have wheezes that mimic asthma, particularly in children

Clinical presentation

- Complete reversal of the circulatory system and the viscera known , including dextrocardia
- Situs inversus has no serious adverse health consequences per se, and the condition often goes undetected until a chest radiograph is obtained.
  - Very useful sign if PCD diagnosis is considered.
  - 50 % of patients with PCD

Dextrocardia



Clinical presentation

- Congenital cardiac anomalies are 200-fold higher in PCD than the general population,in 15%
- Hydrocephalus has been described from several persons with primary ciliary dyskinesia and two siblings with ciliary aplasia . Impaired function of ependymal cilia may be at least partially responsible

Clinical presentation

- Most men with PCD have living but immotile spermatozoa and are infertile.
- Women have decreased fertility, with fewer than 50% successfully completing pregnancy.
- Impaired ciliary function in the fallopian tubules can delay ovum transit leading to reduced fertility or ectopic pregnancy

Diagnosis

- Diagnosis can be difficult..
- no single ‘gold standard’ diagnostic test
- The use of combinations of distinct PCD symptoms and combination of tests conducted in centres with extensive experience of normal and abnormal findings

Diagnosis

- Patients should be tested for PCD if they have several of the following features:
- Persistent wet cough
- Situs anomalies
- Congenital cardiac defects
- Persistent rhinitis
- Chronic middle ear disease with or without hearing loss
- A history in term infants of neonatal upper and/or lower respiratory symptoms

Management

- Saccharin Test:
- The traditional screening modality for PCD. It measures mucociliary clearance by placing a saccharin microtablet onto the anterior head of the inferior turbinate and quantifying the time it takes for the patient to taste the sugar. values shorter than 20 minutes are considered in the normal range.
- The saccharin test is unreliable in children and therefore it is not commonly used during the diagnosis of PCD

Nasal nitric oxide

- is an excellent screening test for patients suspected of PCD
- A nasal catheter is placed through a foam sleeve.. which is used to seal the nostril from the atmosphere and measure the concentration of nitric oxide
- Several studies have demonstrated that patients with PCD will have low levels of nNO, almost always <77 nL·min−1 in PCD
- Therefore, screening results with a low nNO level, require other confirmatory tests, such as ciliary ultrastructure analysis or genetic analysis to confirm PCD

Ciliary Ultrastructure Analysis

- Using transmission electron microscopy
  - Fresh ciliated mucosal biopsies are performed and placed in glutaraldehyde.
  - The preferred mucosal biopsy technique is a brushing from the bronchi and pharynx; however, other options include endoscopic bronchial tissue biopsy or inferior turbinate biopsy.
  - The most common abnormalities include: (a) absence or shortening of dyein arms, (b) absence of radial spokes, and (c) loss of the central pair of microtubules with transposition of a peripheral doublet into the center

Ciliary Motility Analysis

- Fresh respiratory mucosal biopsies are placed in isotonic saline and rapidly transferred to a lab for high-speed video microscopy.
- Cilia are then evaluated for the following beat characteristics: (a) coordination. (b) frequency, and (c) pattern
- This method hasnow been adopted as the gold standard for the assessment of ciliary beat pattern

Genetic analysis

- Can be challenging due to genetic heterogeneity and the extensive size of PCD causing genes.
- At present it is estimated that causative genes can be identified in about 65% of PCD patients
- The two most common genes mutated in PCD include DNAI1 and DNAH5 both of which have been implicated in 30% to 38% of PCD patients

Management

- As there is no cure for PCD, its management aims to optimise health, social and psychological wellbeing, whilst preventing progression of lung damage, with a multidisciplinary team approach. There is, however, a paucity of evidence for optimal management

- Although research is in progress to restore ciliary function using gene and small molecule therapy, it is unlikely that such interventions will be developed for clinical use in the near future

Management

❖ General measures

- Stop smoking
- Adequate nutritional intake and supplementation if necessary
- Immunizations for influenza and pneumococcal pneumonia
- Confirm immunity to measles, pertussis, and rubella
- Patient and family counseling

Management

- Improve airway drainage
- ✓ Chest physiotherapy and chest clearance
- ✓ Mucolytic nebulization
- ✓ Nebulised recombinant human Dnase 2.5 mg daily

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Management

- Others
- Bronchodilators
- oxygen therapy, NIV
- Lung transplant

Management of extrapulmonary complications

- Management of the upper airway
- Includes
  - ✓ Sinonasal irrigation with saline,
  - ✓ Treatment of infections,
  - ✓ Trials of response to nasal steroids and
  - ✓ In refractory cases, consideration of sinus surgery
- Hearing impairment
  - ➢ often requires hearing aids, Insertion of ventilation tubes
- Infertility is common and PCD patients require access to a specialised fertility clinic

Thank you